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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/783,268	02/20/2004	Andrea Savarino	97728.00147	7328

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EXAMINER	
SAMALA, JAGADISHWAR RAO	
ART UNIT	**PAPER NUMBER**
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/783,268	SAVARINO, ANDREA	
	Examiner	Art Unit	
	Jagadishwar R. Samala	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 July 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *12-14 and 28-37* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12-14 and 28-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/5/05;3/15/06 & 12/6/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Receipt is acknowledged of applicant's Response to Restriction Requirement, filed on July 25, 2007 and Information Disclosure Statement (IDS) filed on 03/15/2006, 08/05/2006 and 12/06/2006.

Drawings

The drawing(s) filed on 02/20/2004 has been acknowledged.

Election/Restriction

Applicant's election without traverse of Group II, claims 12-14 and 28-37 in the reply filed on July 25, 2007 id acknowledged.

Claims 1-11, 15-27, and 38-58 are hereby withdrawn from further consideration pursuant to 37 CFR 1.142 (b) as bei9ng drawn to nonelected group, there being no allowable generic or linking claims.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> **The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.**

Claims 12-14 and 28-37 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims because the specification, while being enabling for treating malaria using the compounds as claimed,

does not reasonably provide enablement for preventing malaria using combination of HIV protease inhibitors as claimed.

Attention is directed to Inre Wands, 8 USPQ 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing Ex parte Forman, 230 USPQ 546 (BdApls) at 547 court recited eight factors:

1) The Nature of the invention:

The instant invention is drawn to a method of treating or preventing malaria in humans comprising administering to a patient a composition comprising: at least one of the inhibitors of the HIV protease, in amounts that are therapeutically effective to inhibit the growth of plasmodium sp.

2) The state of prior art:

As the state of art recognizes, malaria is one of the most infectious diseases that has different path-etiologic factors (e.g. bio-pathways and pathogens) involved in. Infection with plasmodium falciparum parasites and plasmodium vinckei etc.

The state of the art recognizes that the significance of particular drug treatment for modifying different aspects of biological activity cannot be predicted a priori and furthermore, the state of the art also recognizes that no single drug is effective for all the pathogens and etiologies causing the malaria disease. Further, a demonstration of prevention is required for the skilled artisan to be able to use the claimed composition for their intended purpose of preventing malaria. Without this demonstration, the skilled artisan would not be able to reasonably predict the outcome of the administration of the

claimed composition, i.e. would not be able to accurately predict if protective immunity has been induced.

Unfortunately, the art is replete with instances where even well characterized antigens that induce an in vitro neutralizing antibody response fail to elicit in vivo protective immunity. See Boslego et al. wherein a single gonococcal pillin protein fails to elicit protective immunity even though a high level of serum antibody response is induced (page 212, bottom of column 2). Accordingly, the art indicates that it would require undue experimentation to formulate and use a successful vaccine without the prior demonstration of vaccine efficacy.

The state of the art with respect to vaccine development against malaria has been difficult. Malaria Vaccine Initiative (MVI) discloses that scientist around the world have searched for a safe and effective malaria vaccine for several decades. The search has proven to be a difficult challenge, due to the complexity of the organism, its ability to change through its life cycle both in the human and in the mosquito, and its ability to hide from the immune system (www. malariavaccine.orq/mal-prevention.htm; see prevention of human disease through use of vaccines)

It is apparent, from the above reports, that protective immune response to malaria are still in the investigation stage and that one skilled in the art would not readily accept claims to vaccines protecting against human malaria, thus generally, art acknowledges that the conditions associated with malaria disease can be reduced or treated but not completed prevented or inhibited because all the possible causes are unknown or completely avoidable. There are no known compounds, which have been

demonstrated to prevent or cure completely a disease (any species of malaria). Since this assertion is contrary to what is known in medicine, proof must be provide that this revolutionary assertion has merits.

3) The relative skill of those in the art:

The relative skill in the art is recognized as high.

4) The predictability of the art:

The high degree of unpredictability in the treatment of the malaria is well known in the art. A slight change in the structure of the drug would drastically change its influence on receptor binding activity. Many times, therapeutic activities or toxic effects are corresponding to dose and selectivity (receptor binding), etc.

Furthermore, a treatment using a pharmaceutical composition containing multiple active ingredients or carriers having different chemical structures and modes of actions, their interaction, co-action, e.g. synergism etc. is even more unpredictable.

5) The breadth of the claims:

Applicant's assertion that the inventive compounds, its composition would be useful for treating the possible malaria disease does not commensurate with the scope of the objective enablement, especially in view of the high degree of unpredictability and the limited working examples.

6) The amount of guidance/working examples:

Insufficient direction or guidance is presented in the specification with regard to a composition for the prevention against malaria. The specification only exemplifies few examples such as an addition of antimalarial agents to IDV might

produce a level of HIV inhibition higher than that produced by IDV alone.(examples 1 and 2). The specification fails to show complete inhibition, which may utilize different combination in the treatment, which may utilize different underlying mechanism (s).

The specification provides lack of evidential support substantially where any skilled artisan cannot clearly understand how the claimed invention is achieved at the time of the invention with the information provided and thus, the claims are considered not enabled with the information given.

7) The quantity of experimentation necessary:

Since insufficient teaching and guidance have been provided in the specification, and the efficacy of the inhibitors of the HIV protease for treating or preventing malaria mentioned above cannot be predicted from a priori but must be determined from the case to case by painstaking experimental study and when the above factors are weighed together, one of ordinary skill in the art would be burdened with undue "painstaking experimentation study" to use the invention commensurate in scope with the claims.

2. Claims 12-14 and 28-37 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a Written Description rejection.

The claimed invention is directed to the treating or preventing malaria comprising administering a composition comprising at least one of the "inhibitors of the HIV protease" that are therapeutically effective to inhibit the growth of plasmodium sp. While the examiner acknowledges that the term " inhibitors of the HIV protease" is mentioned in the instant specification, the term is not defined by the instant specification in a clear and concise manner. The specification discloses examples of structures of some compounds within the scope of what is claimed. However, there is no evidence that there is any per se structure/function relationship between the disclosed HIV protease inhibitor compounds and any others that might be found using the claimed method. Structural identifying characteristics of group of HIV protease inhibitors are not disclosed. Further, there is no description of structural characteristics that are required to retain biological activity. Accordingly, in the absence of sufficient recitation of distinguishing characteristics, the specification does not provide adequate written description of the claimed genera, aside from the specific agents recited in the specification.

Claim Objections

3. Claim 29 is objected to because of the following informalities: there is a typographical error is found in the term (hydroxycloroquine) recited in the claim 29. The said spelling error seems to be inadvertent. Appropriate correction is required..

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> **A person shall be entitled to a patent unless –**
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claims 12-13 are rejected under 35 U.S.C. 102(b) as being anticipated by Liversidge et al. (US 6,221,400 B1).

Claims are drawn to a method of treating or preventing malaria comprising administering a composition comprising at least one of the inhibitors of the HIV protease.

With respect to claims 12-13, Liversidge et al discloses a method of treating mammals comprising administering a pharmaceutical composition comprising nanoparticulate HIV protease inhibitors (see abstract and col. 4, line 43-46). And also discloses the HIV protease inhibitors drug substance such as saquinavir, retinovir, indinavir (see col. 6, lines 36-42).

Claim limitations such as "for preventing malaria infection" are being viewed as an intended use. A recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. Since the compositions

are the same they would necessarily have the same biochemical and immunological properties.

Applicant's attention is directed to *Ex parte Novitski*, 26 USPQ2d 1389 (BOPA 1992) illustrating anticipation resulting from inherent use, absent a *haec verba* recitation for such utility. In the instant application, as in *Ex parte Novitski*, supra, the claims are directed to preventing a malady or disease with old and well known compounds or compositions. It is now well settled law that administering compounds inherently possessing a protective utility anticipates claims directed to such protective use.

Thus, the claims are readily envisaged by the teaching of the cited reference and the claims are properly included in the rejection.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> **(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.**

7. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

8. Claims 12-14 and 28-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Semenov et al. (Antimicrobial agents and Chemotherapy 42, 2254-2258, 1998) or Davis (US 5,278,173) in view of Patel et al. (US 6,265,406 B1) or Johnson et al (US 2002/0177603 A1).

Claims are drawn to a method of treating or preventing malaria comprising administering a composition comprising at least one of the inhibitors of the HIV protease in amount that effective to inhibit the growth of plasmodium sp.

Semenov et al discloses protease inhibitors that have potent antimalarial effects. Semenov et al discloses further protease inhibitors to be used can include L-Transepoxy-succinyl-leucylamido-(4-guanidino)-butane (E-64) among others (page 2254; protease inhibitors). And also, discloses the combination of cysteine and aspartic protease inhibitors have strong antimalarial effects, both against cultured p. calciparum parasites and against murine p. vinckei infections (page 2257; discussion).

Davis discloses a method of administering antimalarial drug to a human in an amount sufficient to prevent or at least inhibit infection of T lymphocytes by HIV in vivo or to prevent or at least inhibit replication of HIV in vivo (see col. 3, lines 4-8). And antimalarial drugs used for the treatment includes quinolinic compounds such as quinine, chloroquine, mefloquine, in the form of the free base or in the form of a pharmaceutically acceptable acid addition salt (see col. 4, lines 1-20). And further, the antimalarial drug is employed in an amount sufficient to provide an adequate concentration of the drug to prevent or at least inhibit infection of T lymphocytes by HIV in vivo (see col.4, lines 65+).

The Semenov and Davis references differs from the instant case only in that they does not include at least one of the inhibitors of the HIV protease and at least one nucleosidic inhibitors of the HIV reverse transcriptase in an amount to inhibit the growth of plasmodium sp.

However, it would have been obvious to one of ordinary skill in the art at the time of the invention to incorporate inhibitors of the HIV protease and at least one nucleosidic inhibitors of the HIV reverse transcriptase in an amount sufficient to inhibit the growth of plasmodium sp, when Semenov or Davis is taken in view of Patel or Johnson, because Patel or Johnson both teaches a method for the treatment of HIV infection comprising administering an amount of the combination of compounds effective to inhibit HIV infection or treat the symptoms of HIV infection in host. The combination of compounds is preferably a synergistic combination and compounds has undergone thru very same mechanism for the treatment of HIV infections.

Patel et al discloses a method of treating HIV infection comprising administering in combination, to a host a therapeutically effective amount of quinolin-2(1H)-ones and derivatives thereof and at least one compound consisting of HIV protease inhibitors and at least one compound consisting of HIV reverse transcriptase inhibitors. (see abstract and col 16. lines 22-29). And the preferred HIV inhibitors include saquinavir, indinavir, ritonavir, nelfinavir, palinavir, amprenavir, and thereof (see col.. 16, lines 34-38), and preferred HIV reverse transcriptase inhibitors include efavirenz, AZT, ddC, ddI, d4T, 3TC delavirdine and thereof (see col. 16, lines 30-34).

Johnson et al discloses a method for treating HIV infection which comprises administering to a host a therapeutically effective combination of tricyclic compound, one or more compounds selected from the group consisting of HIV reverse transcriptase inhibitors and HIV protease inhibitors (see Para. 0024). And also, discloses the HIV protease inhibitors such as saquinavir, ritonavir, indinavir, amprenavir, nelfinavir, palinvavir, and tipranavir and thereof and the nucleosidic inhibitors of HIV reverse transcriptase include, AZT, ddC, ddI, d4T, and 3TC (see Para. 0121 and 0122).

When these references are taken together, one would have been motivated to extend Semenov or Davis's teaching to add additional HIV protease inhibitors and at least one nucleosidic inhibitors of the HIV reverse transcriptase to maximize therapeutic efficacy. As suggested by cited references, one would have reasonably expected successful addition of secondary ingredients (HIV protease inhibitors and at least one nucleosidic inhibitors of the HIV reverse transcriptase) because the effectiveness, extra benefits (i.e. additional inhibitors to further combat HIV infection) and safety are already well proven and are well suggested by latter references cited.

One would have been motivated to do so, with reasonable expectation of success because it is always desirable to have extended therapeutic modalities to improve patient's compliance by enhancing patient satisfaction and increasing the selection option. The techniques and skills required for making such substitution is conventional knowledge or well within the skills of ordinary artisan as evidenced by these references cited.

One would have been motivated to combine these references and make the modification because they are drawn to same technical fields (constituted with same ingredients and share common utilities) and pertinent to the problem which applicant concerns about. MPEP 2141.01 (a).

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jagadishwar R. Samala whose telephone number is (571)272-9927. The examiner can normally be reached on 8.30 A.M to 5.00 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Hartley can be reached on (571)272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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